



Adverse Childhood Experiences and the Risk of Diabetes: Examining the Roles of Depressive Symptoms and Cardiometabolic Dysregulations in the Whitehall II Cohort Study

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Diabetes Care 2018;41:2120–2126 | <https://doi.org/10.2337/dc18-0932>

OBJECTIVE

Adverse childhood experiences (ACEs) are associated with an increased risk of diabetes in adulthood. However, the potential mediating roles of depression and cardiometabolic dysregulations in this association are not clear.

RESEARCH DESIGN AND METHODS

Prospective data were from the Whitehall II cohort study, with the phase 5 assessment (1997–1999) serving as baseline ($n = 5,093$, age range = 44–68 years, 27.3% female). ACEs were retrospectively reported at phase 5. Depressive symptoms (Center for Epidemiologic Studies Depression Scale) and cardiometabolic dysregulations (inflammation, central obesity, HDL cholesterol, triglycerides, impaired fasting glucose, and hypertension) were examined at phase 7 (2002–2004). Incident diabetes was examined at phases 8–11 (2006–2013) via self-report and blood samples. Participants reporting diabetes prior to phase 8 were excluded. Statistical mediation was examined with path analysis using structural equation modeling. ACEs were modeled as an observed continuous variable, whereas depressive symptoms and cardiometabolic dysregulations were modeled as latent variables. Unstandardized probit regression coefficients with 95% CI are reported for mediation analysis.

RESULTS

ACEs were associated with an increased likelihood of diabetes, with every addition of ACE associated with an ~11% increase in odds of diabetes (odds ratio 1.11 [95% CI 1.00, 1.24], $P = 0.048$). In mediation analysis, ACEs were indirectly associated with diabetes via depressive symptoms (indirect effect 0.03 [95% CI 0.02, 0.04], $P < 0.001$) and cardiometabolic dysregulations (indirect effect 0.03 [95% CI 0.01, 0.05], $P = 0.03$).

CONCLUSIONS

This study provides further evidence of the detrimental psychological and physiological effects of ACEs and suggests that depression and cardiometabolic dysregulations may be pathways linking ACEs with diabetes in adulthood.

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Received 27 April 2018 and accepted 16 July 2018.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-0932/-/DC1>.

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Adverse childhood experiences (ACEs), such as physical abuse, household violence, family dysfunction, and parental mental health and substance abuse problems (1), have been linked to the emergence of mental health conditions and chronic physical diseases in adulthood (1–4). ACEs are retrospectively reported by approximately one in two adults in the U.S. (1), U.K. (5), and Canada (6), although prevalence rates differ according to the type of experiences assessed. A dose-response relationship has been found between a greater number of ACE categories reported and an increased likelihood of experiencing chronic diseases (1) and depression (2) in adulthood.

Diabetes is a chronic health condition affecting ~9% of the global population (7), with prevalence rates rapidly rising (8). Recently, the literature relating ACEs to diabetes has been reviewed and suggests that ACEs are associated with an increased risk of diabetes in adulthood (4). For instance, one study conducted across 10 countries in the Americas, Europe, and Asia found that the retrospective reporting of 3 or more ACEs out of a total of 11 surveyed was associated with an ~59% increase in the odds of diabetes in adulthood compared with those without ACEs (9). Another study of low-income primary care patients in the U.S. demonstrated that a greater number of ACEs was associated with an increased risk of diabetes in adulthood in a dose-response manner (10). A meta-analysis of seven cross-sectional and prospective studies found a statistically significant pooled odds ratio (OR) of 1.32 for the association between experiencing one or more ACEs and diabetes (11).

Indirect evidence suggests that depression in adulthood may mediate the association between ACEs and diabetes. Meta-analyses have shown that elevated depressive symptoms or clinical depression are associated with a 24–60% increased risk of developing diabetes compared with low depressive symptoms (12–14). In addition, individuals who experience ACEs are more susceptible to adult mental health conditions (1,2,15). For instance, Felitti et al. (1) found that those with four or more ACEs, out of a total of seven, were 4.6 times more likely to have had a depressive episode in adulthood compared with those

reporting no ACEs. Reporting only one ACE was also associated with a 50% increased likelihood of depression compared with reporting no ACEs in this study. Associations between ACEs and depression in adulthood have been reported by others (2,16–18). Although studies have demonstrated links between ACEs and depression in adulthood, and between depression and the later development of diabetes, it is not clear whether depression mediates the association between ACEs and diabetes in later life. Mediation occurs when one variable is thought to influence variation in an outcome variable indirectly via one or more intervening variables (19). A meta-analysis of the associations between childhood maltreatment and later obesity, a risk factor for diabetes (20), suggested that the strength of this association was attenuated when depression was included as a covariate (21), which might indicate some degree of mediation, although this was not directly examined. Childhood socioeconomic disadvantage has also been found to be associated with increased odds of prediabetes and diabetes via the indirect effects of depression, as well as adult adiposity and physical inactivity (22). However, this association has not yet been examined with a broader range of ACEs.

It has also been posited that ACEs may impact later development of disease via immune and metabolic dysregulations (23). Meta-analyses have shown that the metabolic syndrome, characterized by a cluster of three or more cardiometabolic dysregulations (central obesity, systemic inflammation, adverse triglyceride levels, low HDL cholesterol, hypertension, and impaired fasting blood glucose levels), is associated with an approximately three- to fivefold increased risk of developing diabetes (24). ACEs are associated with metabolic syndrome and a greater likelihood of systemic inflammation in adulthood (15,25). Therefore, cardiometabolic dysregulations may be another pathway linking ACEs with diabetes in adulthood.

Taken together, there is evidence linking ACEs with the risk of diabetes in adulthood, although a better understanding of the potential pathways between ACEs and diabetes is needed. The association between ACEs and diabetes in adulthood might not be due

to a direct effect of ACEs on diabetes but may rather be accounted for by an indirect effect via different psychological and biological pathways. Based on the research findings suggesting that ACEs are associated with depressive symptoms and cardiometabolic dysregulations in adulthood, and that both depressive symptoms and cardiometabolic dysregulations are risk factors for diabetes, we hypothesized that depressive symptoms and cardiometabolic dysregulations may be pathways linking ACEs with the risk of diabetes in later life. However, to our knowledge, no prior studies have simultaneously examined these potential associations in one longitudinal pathway model.

Accordingly, the aim of the current study was to simultaneously examine the potential mediating role of depressive symptoms and cardiometabolic dysregulations in the associations between ACEs and the risk of diabetes with prospective data from the Whitehall II cohort study. Prior studies that have examined ACEs in the Whitehall II cohort study found that maternal separation for 1 year or more during childhood (26) and early life stressors (27) were associated with hypothalamic-pituitary-adrenal axis functioning in adulthood, and that ACEs were associated with an increased risk of hazardous alcohol consumption in midlife in a dose-response manner (28). However, the associations between ACEs and diabetes and potential mediators of these associations were not examined. We tested the hypothesis that depressive symptoms and cardiometabolic dysregulations independently mediate the association between ACEs and incident diabetes in adulthood.

RESEARCH DESIGN AND METHODS

Study Population

Data were from the Whitehall II cohort study, a prospective study of 10,308 British civil servants between the ages of 35 and 55 years that began in 1985. The data collected include questionnaire data (collected every 2–3 years), anthropometric assessments, clinical measures, and biological samples (collected every 5 years). Detailed information about the Whitehall II study design can be found elsewhere (29,30). The study was approved by the University College London ethics committee and participants

provided informed consent at baseline and at each follow-up assessment.

Measures

Diabetes status was assessed using criteria from the American Diabetes Association (31) and was based on either a self-reported physician diagnosis of diabetes, use of antidiabetic medication, fasting plasma glucose levels ≥ 7.0 mmol/L, or a 2-h oral glucose tolerance test ≥ 11.1 mmol/L, observed during at least one follow-up wave.

ACEs were retrospectively reported during the phase 5 assessment with the question “did any of the following things happen during your childhood (that is, up until you were 16)?” Participants responded to each childhood event with “yes” or “no” answers. ACEs included hospitalization for four or more weeks, parental divorce, unintentional parental unemployment, parental mental illness or problematic alcohol consumption, physical abuse by someone close, exposure to frequent parental arguments or fights, being in an orphanage/children’s home, and maternal separation for 1 year or more. A summary score for the total number of ACE categories experienced (0–8) was calculated.

Depression was measured by the Center for Epidemiologic Studies Depression Scale (CES-D) (32). The CES-D is a 20-item scale that assesses the extent to which depressive symptoms were experienced in the past week. Each item is rated on a 0–3 scale, with total possible scores ranging from 0 to 60. Higher scores reflect a greater severity of depressive symptoms. Internal

reliability of the CES-D in the current study sample was good ($\alpha = 0.88$).

Cardiometabolic dysregulations were based on several cardiometabolic characteristics, including central obesity (waist circumference ≥ 102 cm in men and ≥ 88 cm in women), low levels of HDL cholesterol (< 1.03 mmol/L in men and < 1.30 mmol/L in women), high triglyceride levels (> 1.7 mmol/L), poor glycemic control (fasting blood glucose > 5.6 mmol/L), and hypertension (blood pressure $> 130/85$ mmHg), defined according to the criteria for metabolic syndrome (33). Systemic inflammation assessed by C-reactive protein (CRP) levels ≥ 3.0 mg/L was included as an additional cardiometabolic characteristic. Participants with three or more abnormal cardiometabolic characteristics were considered to have cardiometabolic dysregulations (33).

Design

Questions about ACEs were administered during the phase 5 wave of data collection (1997–1999). The CES-D and cardiometabolic risk factors were assessed during the phase 7 wave of data collection (2002–2004). Phase 7 was the first phase to include the CES-D. Incident diabetes was assessed at phase 8 (2006), phase 9 (2007–2009), and phase 11 (2012–2013), hereafter referred to as the follow-up period. Phases 8 and 11 included self-reported assessments of diabetes, but not OGTT, whereas phase 9 included both self-report and OGTT assessments of diabetes. Phase 10 (2011) was not included because it consisted of a pilot study using a smaller sample of participants.

The study population with available data at baseline consisted of participants with complete data on ACEs at phase 5 ($n = 7,100$), CES-D at phase 7 ($n = 6,012$), at least one metabolic risk factor at phase 7 ($n = 7,136$), and without prevalent diabetes at phase 7 or earlier ($n = 570$ excluded), leaving a total baseline sample of $n = 5,206$. A total of 113 (2.2%) participants were considered to have been lost to follow-up because they did not have information on diabetes status at any of the phases 8–11. The final sample included in the current study was thus $n = 5,093$. Descriptions of the included sample and the complete Whitehall II baseline sample (phase 5 for the current study) are presented in Table 1.

Statistical Analysis

Descriptive and frequency statistics were generated for continuous and categorical sociodemographic and lifestyle variables. Univariate associations between depressive symptoms, metabolic risk factors, and ACEs were examined using logistic and linear regression analysis. ORs or unstandardized regression coefficients with 95% CI are reported for binary outcomes and continuous outcomes, respectively.

To examine statistical mediation, a path analysis using structural equation modeling with mean- and variance-adjusted weighted least squares with robust SE (WLSMV) estimation, which can handle nonnormally distributed data (34), and θ parametrization was used. The model tested the direct effect of ACEs at phase 5 and the risk of diabetes at follow-up, as well as the indirect

Table 1—Whitehall II cohort study participant characteristics at baseline

Characteristic	Phase 5: sample included in the current study ($n = 5,093$)	Phase 5: complete sample ($n = 7,870$)
Age, years	55.4 (5.9), 44–68	56.0 (6.0), 44–69
Female sex	1,389 (27.3)	2,397 (30.5)
White ethnicity	4,782 (93.9)	7,186 (91.4)
Married/common-law	3,924 (79.9)	5,425 (78.4)
High school diploma or higher degree	3,271 (65.0)	4,724 (62.2)
Currently smoke	458 (9.1)	760 (10.5)
Alcohol use frequency daily or more	2,045 (40.7)	3,143 (44.6)
Sleep 6 h or less per average weeknight	2,004 (39.8)	2,928 (41.2)
BMI, kg/m ²	26.0 (3.8), 16–48	26.2 (4.0), 15–48
Parental history of diabetes	407 (8.4)	733 (9.8)

Data for age and BMI are presented as means (SD), range. All other data are presented as n (%).

effect of ACEs on the risk of diabetes in adulthood via depressive symptoms and cardiometabolic dysregulations at phase 7 (34). ACEs were modeled as a continuous variable. Cardiometabolic dysregulations were modeled as a latent variable based on the indicator variables CRP, waist circumference, HDL cholesterol, high triglycerides, impaired fasting glucose, and hypertension. Depressive symptoms were modeled as a latent variable based on each of the 20 CES-D items as indicator variables. A latent variable approach was chosen, as latent variables reduce measurement error and allow for variable reduction (35). A path model was first conducted to estimate the indirect effect of depressive symptoms in the association between

ACEs and diabetes, without cardiometabolic dysregulations included in the model. A second model estimated the indirect effect of cardiometabolic dysregulations in the association between ACEs and diabetes, without depressive symptoms included in the model. A final model simultaneously estimated the indirect effects of depressive symptoms and cardiometabolic dysregulations in the association between ACEs and diabetes (Fig. 1). Unstandardized probit regression coefficients with 95% CIs are reported (34). Good model fit was indicated by a comparative fit index (CFI) value ≥ 0.90 and a root mean square error of approximation (RMSEA) ≤ 0.08 (36). Model paths were adjusted for age and sex. Analyses were conducted

using Stata version 14.0 and MPlus version 7.4 (37).

RESULTS

The average age of the sample was 55.4 years (SD 5.9) at the phase 5 baseline assessment, and 27.3% ($n = 1,389$) were female. The average follow-up time was 8.7 years (SD 1.5). Sociodemographic and lifestyle characteristics of the sample are presented in Table 1.

A total of 344 (6.75%) participants developed diabetes during the follow-up period. The number of ACEs experienced ranged from zero to seven, with 43.8% ($n = 2,232$) of the sample experiencing at least one ACE and 1.8% ($n = 89$) experiencing four or more ACEs. Table 2 describes the proportions of each ACE

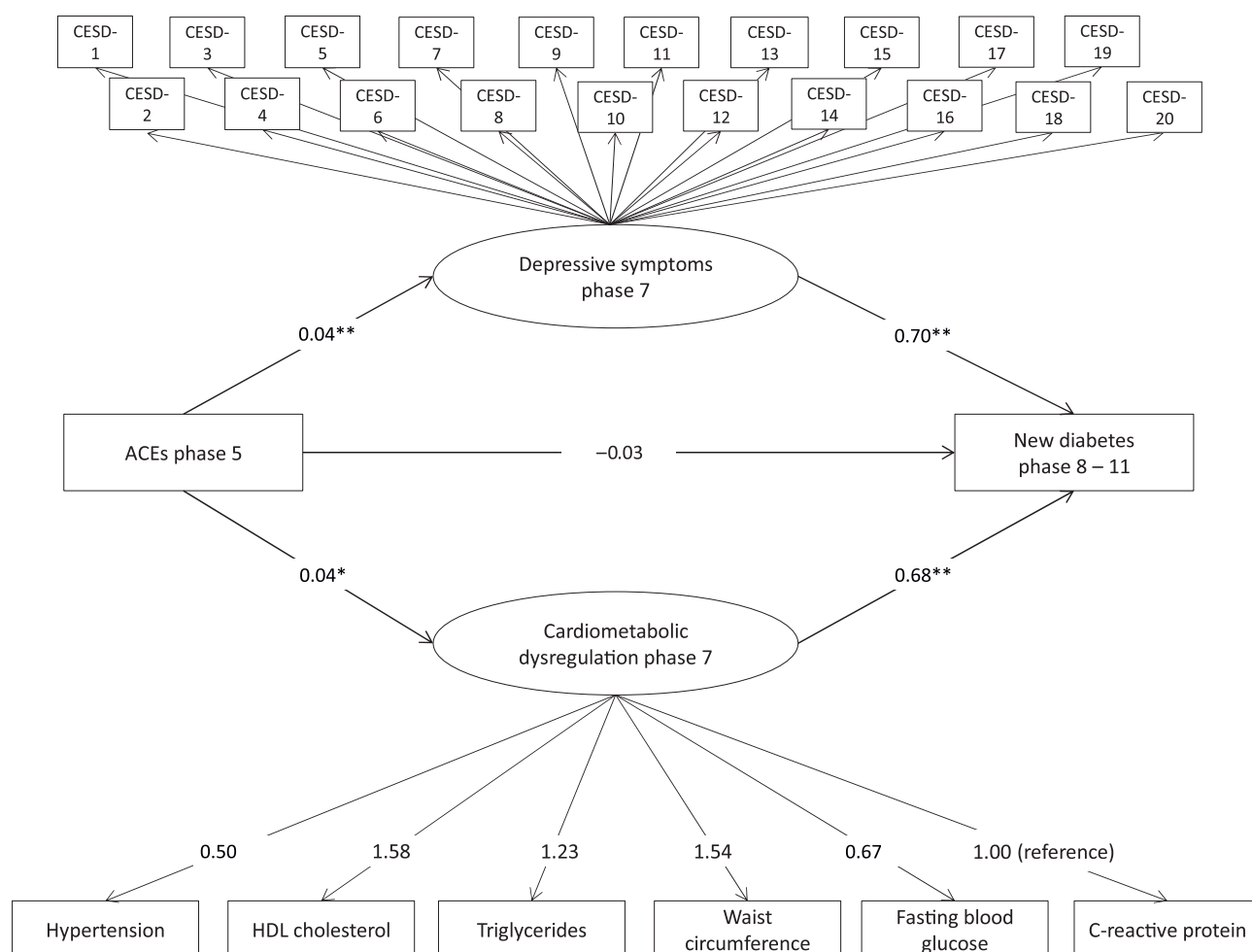


Figure 1—Results of the mediation model for the association between ACEs and the risk of diabetes in adulthood as simultaneously mediated by depressive symptoms and cardiometabolic dysregulations in adulthood. Values are unstandardized probit regression coefficients. A variable presented in a circle represents a latent variable, whereas a variable presented in a rectangle represents an observed variable. The indirect path of ACEs to diabetes via depressive symptoms was statistically significant (0.03 [95% CI 0.02, 0.04], $P < 0.001$), as was the indirect path of ACEs to diabetes via cardiometabolic dysregulations (0.03 [95% CI 0.01, 0.05], $P = 0.03$). Model paths control for age and sex. A sensitivity analysis that included a covariance between depressive symptoms and cardiometabolic dysregulations demonstrated poorer model fit than the main model, although interpretation of path coefficients for mediation analysis was similar to that in the main model. * $P < 0.05$; ** $P < 0.01$.

Table 2—Proportion of each ACE reported

ACE category	<i>n</i> (%)
Parental arguments	973 (19.8)
Parental divorce	202 (4.1)
Parental mental illness or alcohol abuse	309 (6.3)
Parental unemployment	521 (10.6)
Physical abuse	119 (2.4)
Long-term hospitalization (4 weeks or more)	612 (12.4)
Orphanage during childhood	73 (1.5)
Separated from mother for 1 year or more	603 (11.9)

category endorsed. The ACE category most frequently endorsed was parental arguments (19.8%), and the ACE category least frequently endorsed was having lived in an orphanage during childhood (1.5%). The strongest association between each ACE category was found between parental arguments and parental mental illness or alcohol abuse (see Supplementary Table 1 for correlations between each ACE category). The mean depressive symptom score was 7.90 (SD 7.59, range 0–60). A total of 719 (14.12%) participants had at least three cardiometabolic dysregulations (20% had high CRP, 21% had high fasting blood glucose, 21% had high triglycerides, 41% had hypertension, 10% had low HDL cholesterol, and 16% had a high waist circumference).

In unadjusted analyses, ACEs were associated with an increased likelihood of developing diabetes during the follow-up period, with every addition of ACE associated with an ~11% increased odds of diabetes (OR 1.11 [95% CI 1.00, 1.24], $P = 0.048$). A greater number of ACEs was also associated with increased depressive symptoms ($b = 0.02$ [95% CI 0.01, 0.02], $P < 0.001$). The association between ACEs and cardiometabolic dysregulations defined by the metabolic syndrome was not statistically significant, although it was in the direction indicative of risk (OR 1.07 [95% CI 0.99, 1.16], $P = 0.087$). Continuous increases in depressive symptom scores were associated with incident diabetes (OR 1.02 [95% CI 1.01, 1.04], $P = 0.002$), and cardiometabolic abnormalities defined by the metabolic syndrome were associated with an ~5.7 times increased likelihood of diabetes (OR 5.68 [95% CI 4.51, 7.15], $P < 0.001$). When cardiometabolic dysregulations were modeled as a latent variable in a regression analysis, significant associations were

found between cardiometabolic dysregulations and ACEs ($b = 0.02$, $P = 0.05$) as well as diabetes ($b = 1.80$, $P < 0.001$). Similarly, when depressive symptoms were modeled as a latent variable in a regression analysis, significant associations were found between depressive symptoms and ACEs ($b = 0.04$, $P < 0.001$) as well as diabetes ($b = 0.03$, $P = 0.004$).

Mediation Model With Depressive Symptoms Only

Results of the mediation model conducted with depressive symptoms as the only potential mediator included in the model demonstrated that ACEs were indirectly associated with an increased risk of diabetes in adulthood via depressive symptoms. ACEs were positively associated with depressive symptoms (path coefficient 0.04 [95% CI 0.03, 0.05], $P < 0.001$), and depressive symptoms were associated with an increased risk of diabetes (path coefficient 0.32 [95% CI 0.15, 0.48], $P = 0.001$). The indirect effect of depressive symptoms (indirect effect 0.01 [95% CI 0.01, 0.02], $P = 0.002$) was statistically significant. In addition, there was no evidence that ACEs were directly associated with the risk of diabetes in adulthood independent of the effect via depressive symptoms (direct effect 0.04 [95% CI –0.01, 0.08], $P = 0.20$). Model fit was poor (RMSEA = 0.07, CFI = 0.79).

Mediation Model With Cardiometabolic Dysregulations Only

Results of a mediation model conducted with cardiometabolic dysregulations as the only potential mediator included in the model demonstrated that ACEs were indirectly associated with an increased risk of diabetes in adulthood via cardiometabolic dysregulations. ACEs were positively associated

with cardiometabolic dysregulations (path coefficient 0.03 [95% CI 0.01, 0.05], $P = 0.04$), and cardiometabolic dysregulations were associated with an increased risk of diabetes (path coefficient 0.69 [95% CI 0.48, 0.89], $P < 0.001$). The indirect effect of cardiometabolic dysregulations (indirect effect 0.02 [95% CI 0.003, 0.032], $P = 0.05$) was statistically significant. There was no evidence that ACEs were directly associated with the risk of diabetes in adulthood independent of the effect via cardiometabolic dysregulations (direct effect 0.01 [95% CI –0.03, 0.05], $P = 0.64$). Indicators of model fit were adequate (RMSEA = 0.05, CFI = 0.89).

Full Mediation Model

When depressive symptoms and cardiometabolic dysregulations were simultaneously included in the path analysis model, ACEs were found to be indirectly associated with an increased risk of diabetes via both depressive symptoms and cardiometabolic dysregulations (Fig. 1). ACEs were positively associated with depressive symptoms (path coefficient 0.04 [95% CI 0.03, 0.05], $P < 0.001$) and cardiometabolic dysregulations (path coefficient 0.04 [95% CI 0.01, 0.06], $P = 0.02$). Depressive symptoms (path coefficient 0.70 [95% CI 0.57, 0.83], $P < 0.001$) and cardiometabolic dysregulations (path coefficient 0.68 [95% CI 0.48, 0.88], $P < 0.001$) were, in turn, associated with an increased risk of diabetes. Indirect effects for depressive symptoms (indirect effect 0.03 [95% CI 0.02, 0.04], $P < 0.001$) and cardiometabolic dysregulations (indirect effect 0.03 [95% CI 0.01, 0.05], $P = 0.03$) were both statistically significant. There was no evidence that ACEs were directly associated with the risk of diabetes in adulthood independent of the effects via depressive symptoms and cardiometabolic dysregulations (direct effect –0.03 [95% CI –0.07, 0.02], $P = 0.33$). Indicators of model fit were good (RMSEA = 0.04, CFI = 0.90).

CONCLUSIONS

The goal of the current study was to examine the potential roles of depressive symptoms and cardiometabolic dysregulations as mediators of the association between ACEs and incident diabetes in adulthood. To our knowledge, this was the first study to

simultaneously examine psychological and biological pathways linking ACEs with diabetes in adulthood in one model using data from a large prospective cohort study. Overall, we found that cumulative exposure to adverse events during childhood was indirectly associated with an increased likelihood of diabetes in adulthood via the pathways of depressive symptoms and cardiometabolic dysregulations.

The findings of the current study are in accordance with the biological embedding of the childhood adversity model (23,38). The model stipulates that childhood stress, which can arrive from ACEs, programs immune cells with a proinflammatory tendency that in turn predisposes individuals to experience exaggerated biological responses to challenge, as well as predisposes individuals to poorer self-regulation capabilities and a hypervigilance for threat, leading to unhealthy lifestyle behaviors and autonomic and endocrine dysregulation. These factors together contribute to the development of chronic disease. Neurodevelopmental changes can also occur as a result of ACEs, which can contribute to later depression (23).

We also found that for every increase in the number of ACEs, the risk of diabetes increased by 11%. This finding is consistent with the effect size reported by Lynch et al. (10). In our study, we found that 44% of participants experienced at least one ACE, which is generally consistent with other reports. For instance, a study from the U.S. found that 58.5% reported the occurrence of at least one ACE (39). With regard to specific ACE categories, we found that only ~2% of participants reported having been physically abused during childhood, and ~6% reported parental mental illness or alcohol use problems. Felitti et al. (1) found that ~9.6% of participants reported being hit so hard that there were marks or substantial injury by a parent or other adult in the household. They also found that ~23.5% of participants reported having a household member with alcohol problems and 17.5% with mental illness. Differences in the types of questions asked may account for discrepancies across findings.

Limitations

There were several limitations to the current study. First, the definition of

ACEs included in the current study was relatively narrow and did not include events such as sexual or emotional abuse. The ACE assessment also did not include any detail about the age at which the adverse events were experienced. The lack of cohesion between studies on ACE categories makes it difficult to directly compare results with prior studies, particularly with regards to prevalence rates of ACEs. Nevertheless, our results are consistent with prior studies reporting positive associations between ACEs and diabetes in adulthood (4). In addition, the reporting of ACEs was retrospective, and thus potential recall bias is another important limitation. It is also possible that the reported ACEs may have been partially dependent on current emotional state. Long-term follow-up studies with ACEs assessed during childhood are needed to better examine the pathways leading from ACEs to chronic diseases in adulthood. Another limitation was that lifestyle behaviors were not explored as an additional potential pathway linking ACEs with diabetes in the current study. ACEs have been associated with unhealthy lifestyle behaviors such as smoking and excessive alcohol use (40) and might be another mediating pathway linking ACEs with diabetes. The mediation analysis potentially included participants with only one indicator of metabolic dysregulation, which is another limitation. Finally, although most incident cases of diabetes were likely type 2 diabetes due to the age of the sample, we cannot rule out the possibility that incident cases of diabetes also included type 1 diabetes. Despite these limitations, the current study contributes to the existing literature by directly testing a longitudinal path model in a large sample of middle-aged adults to gain further insight into the potential pathways linking ACEs with diabetes in adulthood.

Conclusion

This study contributes to the limited longitudinal research on psychological and biological pathways linking ACEs with chronic health conditions in adulthood with the use of a large prospective cohort study. Identifying psychological and biological pathways through which ACEs increase the risk of diabetes can help to identify potential targets for

intervention and help improve our basic understanding of the pathways linking environment, mental health, and physical health. Although the observational nature of the current study limits the direct clinical implications of these findings, our study might suggest that early intervention targeting depressive symptoms and cardiometabolic dysregulations for individuals who have experienced ACEs may help prevent the onset of diabetes. Overall, the current study provides further evidence of the detrimental psychological and physiological effects of ACEs and suggests that depression and cardiometabolic dysregulations may be pathways linking ACEs with diabetes in adulthood.

Acknowledgments. The authors thank all of the participating civil service departments and their welfare, personnel, and establishment officers; the British Occupational Health and Safety Agency; the British Council of Civil Service Unions; all participating civil servants in the Whitehall II study; and all members of the Whitehall II study team. The Whitehall II study team comprises research scientists, statisticians, study coordinators, nurses, data managers, administrative assistants, and data entry staff, who make the study possible.

Funding. The Whitehall II study is supported by grants from the U.S. National Institute on Aging (R56AG056477 and R01AG034454) and the U.K. Medical Research Council (MRC) (K013351 and R024227). S.S.D. is supported by a postdoctoral fellowship from the Canadian Institutes of Health Research. E.G. is supported by a doctoral fellowship from the Canadian Institutes of Health Research. M.K. is supported by the MRC, the Academy of Finland (331492), and NordForsk.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.S.D. researched data and wrote the manuscript. E.G., M.K., and N.S. reviewed and edited the manuscript and contributed to discussion. All authors provided intellectual input and approved the final version of the manuscript. S.S.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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